



Diagnosis and Management of DSD in the United Kingdom

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Conflict of interest disclosure

- Invited lectures
 - Merck
 - Sandoz
 - Diurnal
- International paediatric endocrine nurse advisory board
 - Merck

Introduction

- Introduction to DSD
- Classification
- Embryology reminder
- Chromosomes reminder
- What is a DSD
- MDT approach in the UK
- Diagnostic process in the UK
- The CNS role in DSD
- UK statistics
- International differences
- Education and Support



What is a DSD?

- Congenital conditions in which development of chromosomal, gonadal or anatomic sex is atypical
- True genital ambiguity
 - 1 in 5000 / 1 in 4500 births
- Genital anomalies
 - 1 in 300 births



Revised nomenclature: Chicago Consensus 2006

Previous	Revised
Intersex	Disorders of sex development (DSDs)
Male pseudohermaphrodite	
Undervirilization of an XY male	46,XY DSD
Undermasculinization of an XY male	
Female pseudohermaphrodite	
Overvirilization of an XX female	46,XX DSD
Masculinization of an XX female	
True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

Classification of DSD

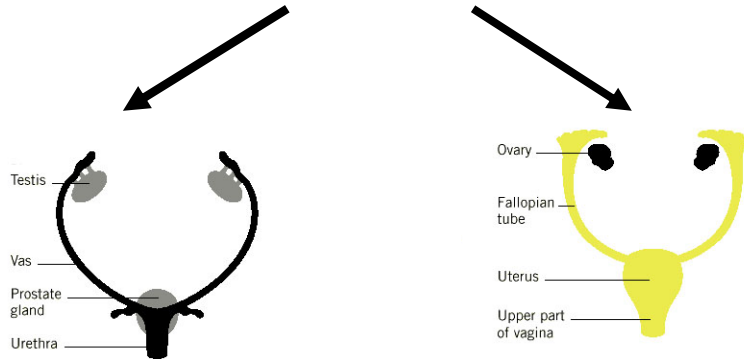
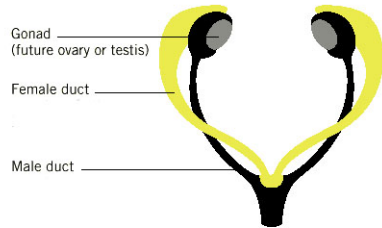
- **46,XY DSD (under virilised genetic male)**
 - Disorders of testicular development
 - Ovotesticular DSD
 - Disorders of androgen synthesis / action
 - Complete Androgen Insensitivity Syndrome
 - Others
 - Hypospadias
- **46,XX DSD (over virilised genetic female)**
 - Disorders of ovarian development
 - Ovotesticular DSD
 - Androgen excess
 - Congenital Adrenal Hyperplasia

- **Sex chromosome DSD (variable)**
 - Turner syndrome
 - Klinefelter syndrome
 - Mixed gonadal dysgenesis



Endocrinology in sex development

Formation of internal structures



- **Foetal ovaries**

- Make small amounts of testosterone and AMH (anti Mullerian hormone)

- **Foetal testes**

- Make lots of both hormones
- The presence or absence of these hormones influences the development of the internal sex ducts:

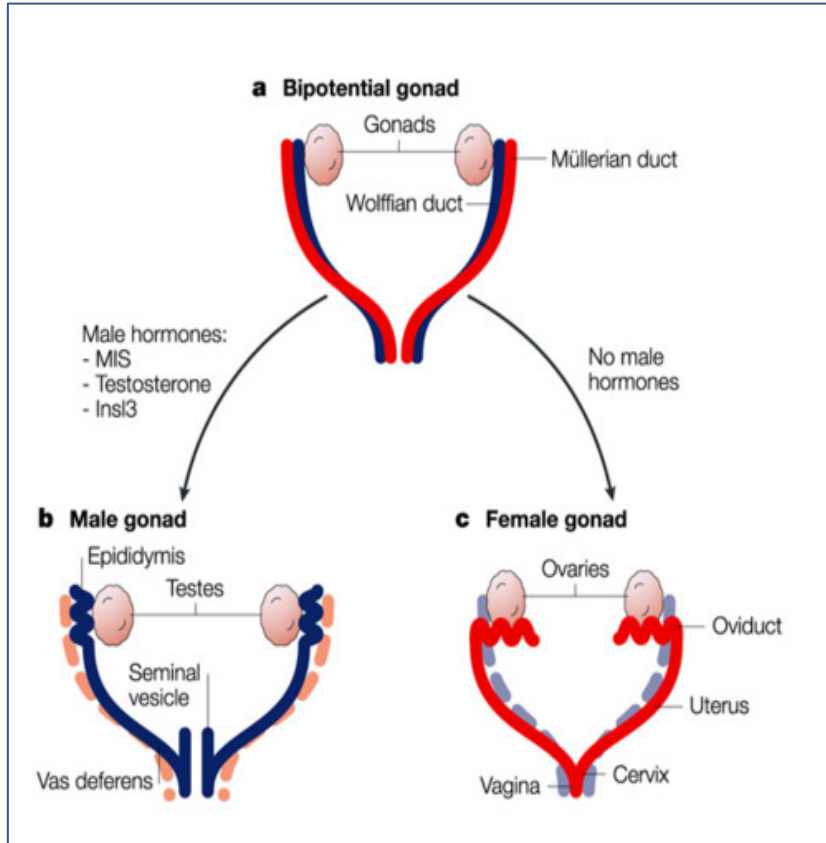
- **Mullerian ducts**

- Found in boy and girl fetuses, but disappear in boys when the testes make AMH (Mullerian Inhibiting Hormone)
- Forerunners of the uterus, cervix, fallopian tubes and upper portion of the vagina

- **Wolffian ducts**

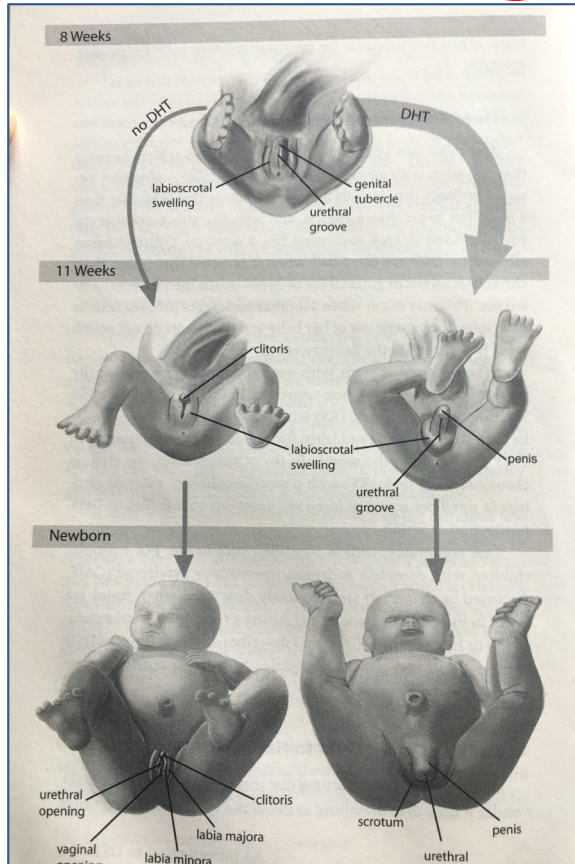
- Found in all fetuses but disappear in girls as they have no testes to produce testosterone
- Forerunners of vas deferens, epididymides, prostate gland and seminal vesicles

Genitalia development – 7-8 weeks



- **7-8 weeks**
 - Presence of XY chromosome
 - Triggers activation of SRY gene
 - Initiates development of a testis
 - Primary sex chords develop into Sertoli cells
 - AMH
 - Leads to regression of the Mullerian duct
 - Leydig cells produce testosterone
 - Stimulate Wolffian duct to form epididymis, vas deferens and seminal vesicles

External genitalia development



- A baby who doesn't make a byproduct of testosterone called dihydrotestosterone (DHT) will grow a vulva
- If a baby does make DHT, they will grow a penis and scrotum
- DHT is made in our bodies when an enzyme called 5α reductase is available
 - This changes T to DHT

Different DSD

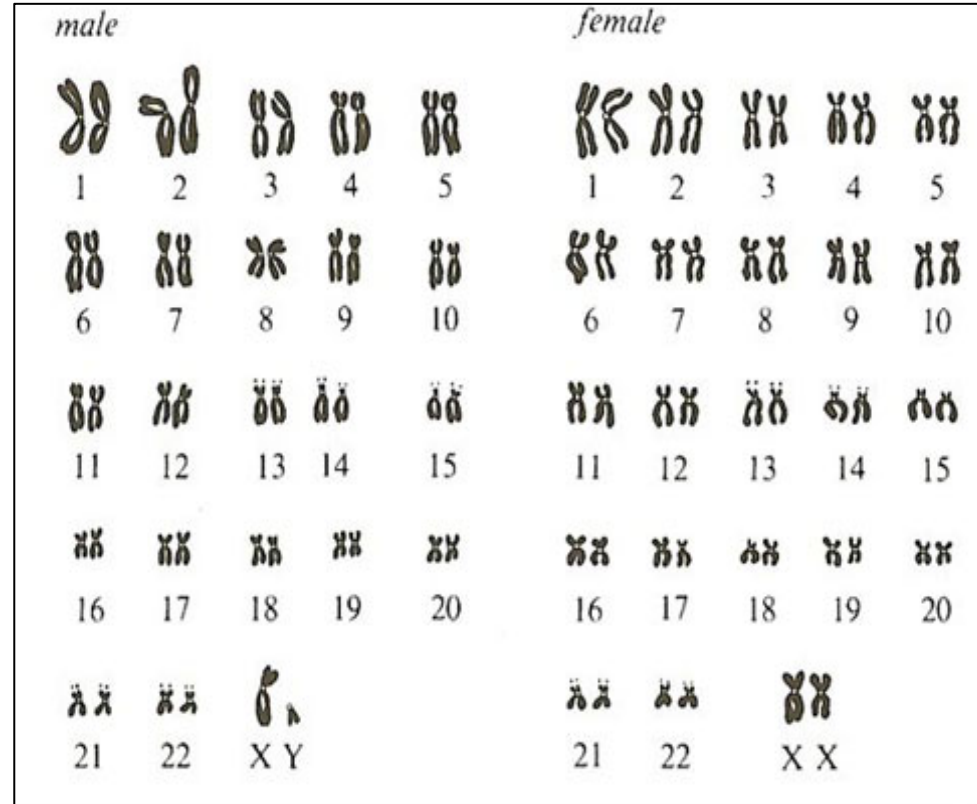
- 46 XY DSD
- 46 XX DSD
- Sex chromosome DSD



XX and XY chromosomes

- XX – genotypic female
- XY – genotypic male
- Half of sperm cells carry the X chromosome, and half carry the Y chromosome
- The SRY gene present on the Y chromosome will act as a signal for the pathway for maleness
 - Starts off virilisation
- Can also have a chromosomal arrangement that is contrary to phenotypic sex
 - XX males
 - XY females
 - Abnormal number of sex chromosomes may be present

• DSD



Clinical Examination

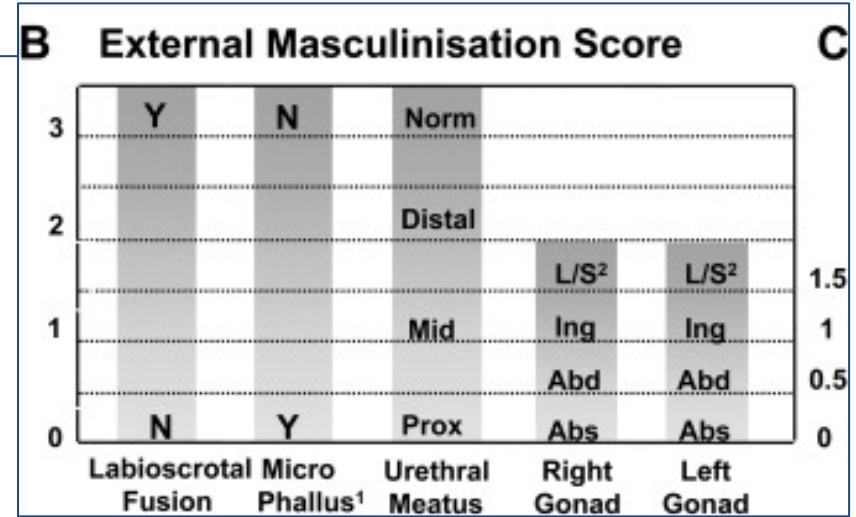
- Thorough general physical examination
 - Any dysmorphic features
 - Syndromes associated with DSD
 - Signs of systemic illness
 - Metabolic problems



- Genital examination
 - Urethral opening position
 - Palpable gonads outside inguinal canal / Labio-scrotal folds
 - Usually be testes
 - Anogenital distance
 - Degree of rugosity
 - Pigmentation of labio / scrotal tissue
 - Virilisation

Clinical Rating Scales

- External Masculinisation Scale
 - Score of < 7 is considered ambiguous
- Virilisation of XX individuals (Prader)



Normal ♀



I



II



III



IV



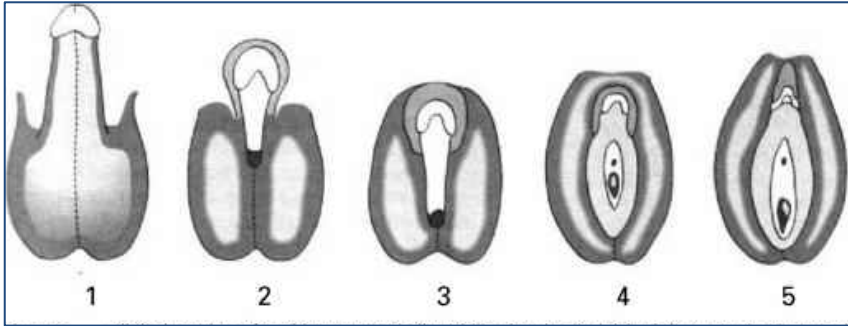
V



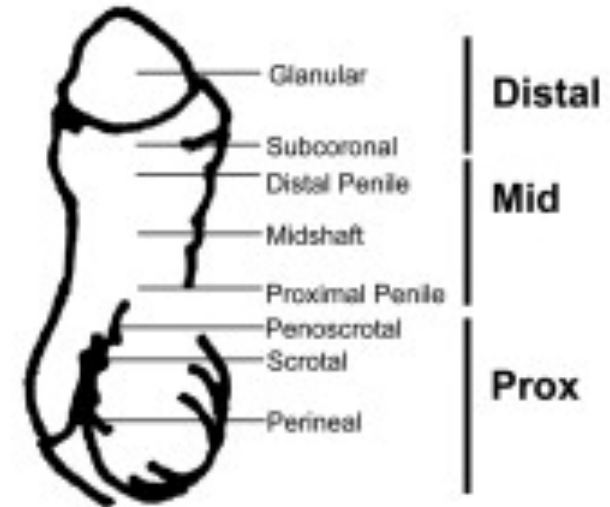
Normal ♂

Clinical Rating Scales

- Androgen Insensitivity (Quigley)



- Hypospadias classification



46XY DSD - Presentation

- Absence of secondary sexual characteristics in an adolescent boy
- Hypospadias
- Ambiguous genitalia at birth
- Primary amenorrhea in an adolescent child with a complete female phenotype
- Variation depends on 2 factors:
 - Degree in disturbance of androgen production or action
 - Point at which this disturbance occurs during sex development
- Anatomic presentation can be classified by using clinical rating scales

46XY- Androgen Insensitivity Syndrome

- *Complete* absence of androgen action from the time of early foetal development results in a child with a typical female external phenotype (CAIS)
- *Partial* action of androgens during foetal development causes hypospadias (PAIS)
 - Micropenis can occur
 - Cryptorchidism
- Mullerian structures may be present or absent
 - If AMH not released, then internal structures may remain as female
 - Must determine if present as will have a bearing on fertility if raised female
- Gonadal germ cell cancer risk
 - Increased in testes with impaired development and presence of Y chromosome material
 - PAIS and raised as male – strict cancer surveillance
 - CAIS and raised as female – prophylactic gonadectomy - ? Childhood / Puberty

Model Hanne Gaby Odiele reveals she is intersex to 'break taboo'

🕒 24 January 2017 | Europe

🔗 Share



Hanne Gaby Odiele had two major operations, as a child and a teenager

A top fashion model has revealed that she is intersex, saying that speaking out will help break a taboo.

Hanne Gaby Odiele, 29, was born with undescended testicles, which were removed when she was 10 after doctors warned that they could cause cancer.

Intersex people are born with a mixture of male and female sex characteristics.

According to the United Nations, the condition affects up to 1.7% of the world population.

Ms Odiele, originally from Belgium, was born with androgen insensitivity syndrome (AIS).

Supermodel comes out as intersex: 'My body isn't really male or female,' Hanne Gaby Odiele reveals

Supermodel wants to break the 'taboo' surrounding the syndrome of being born with sex characteristics that aren't entirely male or female



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FIT NOTES
THIS IS HOW WE (FOAM) ROLL

Travelling?
WE'LL HELP YOU PACK IN STYLE
PLUS essential summer sunnies

TREVOR NOAH
ON LIFE IN THE US, THESE CRAZY ELECTIONS AND LOVE

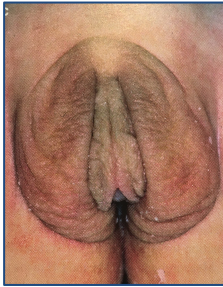
CASTER SEMENYA

TOTALLY CONFIDENT, SERIOUSLY INSPIRING AND FUNNY



CAIS / PAIS

- PAIS
 - Showing minimal virilisation of phallus and genital folds



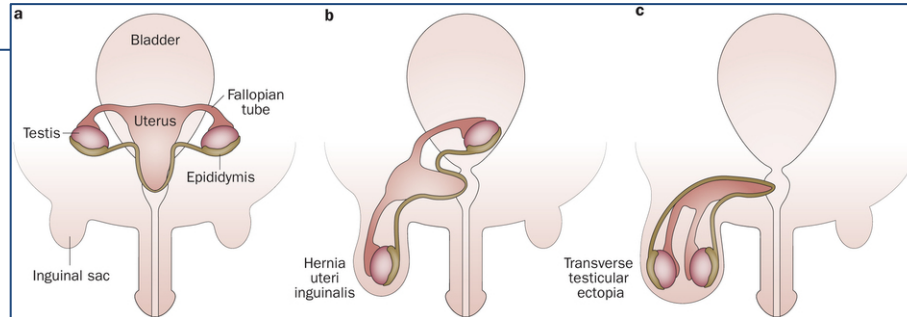
- More virilised, where the genitalia show unfused labio-scrotal folds, but pigmentation and wrinkling more noticeable, with a larger phallus



- CAIS
 - Showing normal female external genitalia, but visible gonads in the groin

46XY - Persistent Mullerian Duct Syndrome

- Mutations in the gene encoding AMH
 - Lead to persistence of Mullerian duct organs in a 46XY individual
- Usually present
 - Cryptorchidism
 - Uterine remnants only apparent on examination, or later inguinal herniation



46XY Gonadal Dysgenesis

- This occurs when there is disruption in the testicular developmental pathway toward mature Sertoli and Leydig cells
- Usually leads to:
 - Small testes with poor androgen-production capacity
 - Presence of mullerian structures
 - Elevated gonadotrophins from puberty
 - Primary gonadal failure
 - Inadequate early androgen production leading to bifid scrotum and severe chordee of phallus



46XX Presentation

- Ambiguous genitalia
 - More than half of all infants born with AG are 46XX
 - Due to in utero exposure of androgens
 - Source may be adrenal (CAH) or testicular
- Complex congenital malformations
 - Cloacal extrophy, or bladder extrophy
- Gradual clitoris enlargements during childhood
 - Non classical CAH
- Abnormal developments at puberty
 - Primary amenorrhoea
 - No breast or pubic hair development (46XX gonadal dysgenesis or steroid biosynthetic defects) OR
 - Normal breast and pubic hair development (Mullerian duct agenesis)
 - Normal breast development but little or no pubic hair (CAIS)

46XX CAH



- Baby will have been exposed to excess male hormone in-utero
- The genitalia will look like a boy's:
 - Labia will fuse to look like a scrotum
 - Clitoris enlarges and looks like a penis
- Can sometimes be so severe, sex assignment is difficult
 - Need karyotype
 - Will still have normal internal structures
 - Surgery may be needed to correct outer appearance
 - CONTROVERSIAL

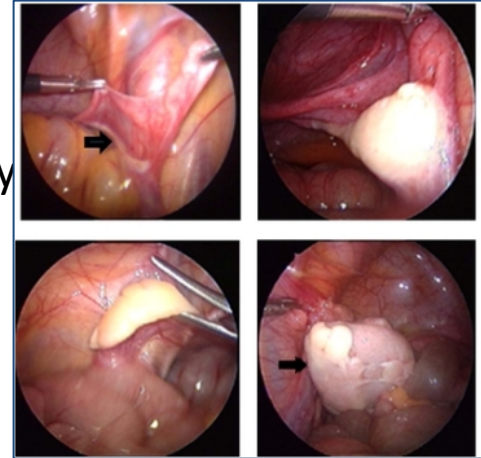


- Exposure to prenatal androgens and Prader 3 virilisation at birth
- Same baby at age 8 weeks at the time of genital reconstruction, showing some regression of virilisation after starting steroid treatment
- Another baby girl with a more severe form of 21OHD, leading to more severe virilisation (Prader IV)



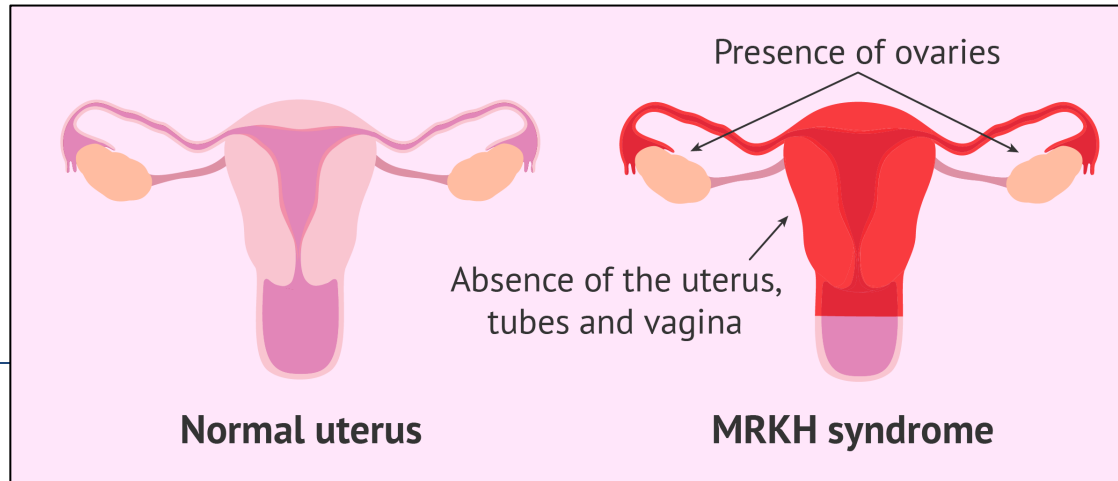
46XX Gonadal Dysgenesis

- Mutations in FSH receptor gene has been identified
- 'Pure' without features of TS
- Streak gonads are present due to germ cells not forming properly
 - Mostly composed of fibrous tissue
- Characterised by primary amenorrhoea with or without secondary sexual characteristics



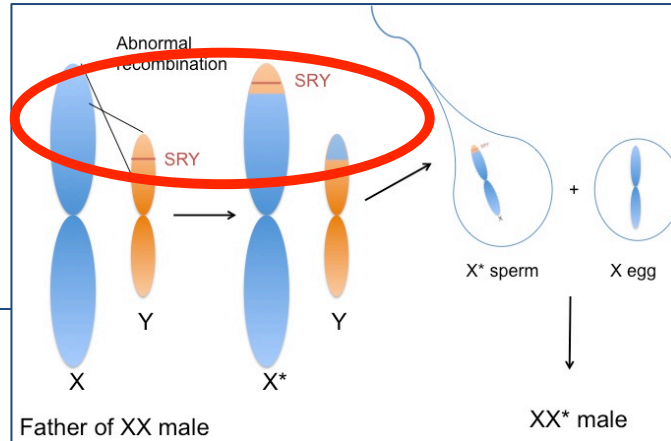
46XX Mullerian Duct Aggenesis

- Vaginal agenesis usually associated with an absent uterus and fallopian tubes but with normal ovarian development
 - Mayer–Rokitansky–Küster–Hauser syndrome



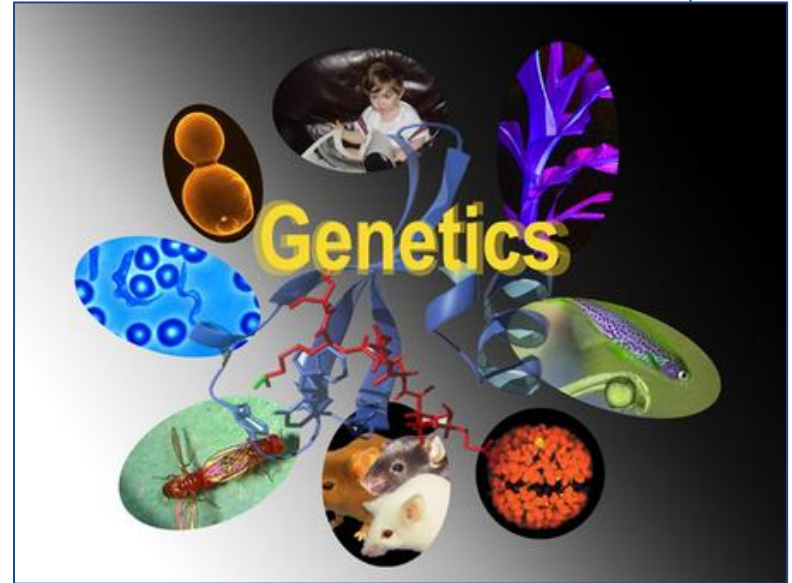
46XX Testicular DSD

- 1 in every 20,000 males with testes has a 46XX karyotype
- Translocation of SRY to the tip of one of the X chromosomes has occurred
- Phenotypical similarities between 46XX men and those with Klinefelter Syndrome
 - 46XX men shorter



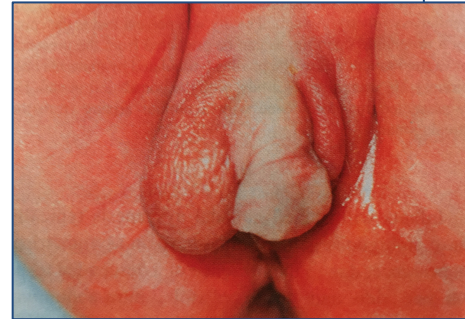
Sex Chromosome DSD

- 46XX Ovo-testicular DSD
- Klinefelter Syndrome
- Turner Syndrome
- 45X / 46XY



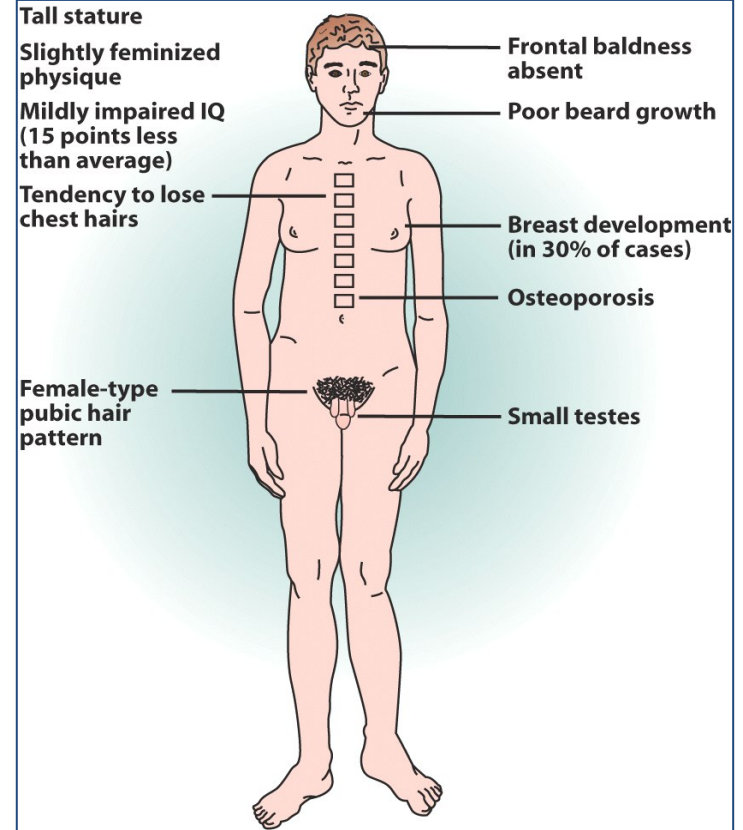
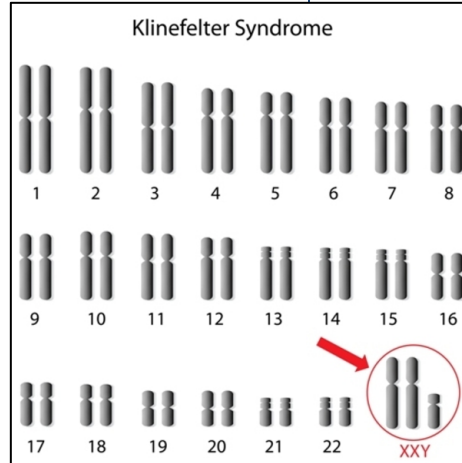
46XX Ovo-Testicular DSD

- Specific type of gonadal dysgenesis
 - Presence of ovarian follicles and seminiferous tubules in the gonads
- Distribution in the gonads vary
 - 89% of ovotestes, ovarian and testicular elements are evenly distributed
- Testicular tissue undergoes atresia at a faster rate than ovarian tissue
- Phenotype varies
 - Often testis on right and ovary on left
- Small number of women can become mothers
- Paternity never reported
 - Gonad most likely to function will be the ovary
 - Gonadal cancer risk in 46XX ovo-testicular DSD is low risk
 - May be fertile oocytes
 - Spermatogenesis absent



Klinefelter syndrome 47XXY

- Affects sexual development
 - Testes don't fully develop
 - Oligospermic
 - Lower levels of testosterone
- Taller than average
- Many men only discover this when they seek help for infertility



Turner syndrome

- Only affects girls
- Affects growth and sexual development
 - Ovaries aren't developed properly
- In TS the second sex chromosome is either:
 - Completely absent (45,X) (Monosomy X)
 - Partially absent
 - Forms an isochromosome (isoXq), possessing a long arm duplication (q) and being devoid of a short arm (p)
 - In a ring formation (rX)
 - Is devoid of the homeobox gene, **SHOX** (short stature homeobox)
- Any of these variations of the second sex chromosome may occur with or without cell line **mosaicism**
 - Missing the X in only some of the cells
 - May have fewer symptoms



Completely absent
(45,X)



Partially absent



Forms an
isochromosome
(isoXq)



Ring formation (rX)



Deletion of SHOX gene
prior to the junction
between Xp22.2 and Xp22.3

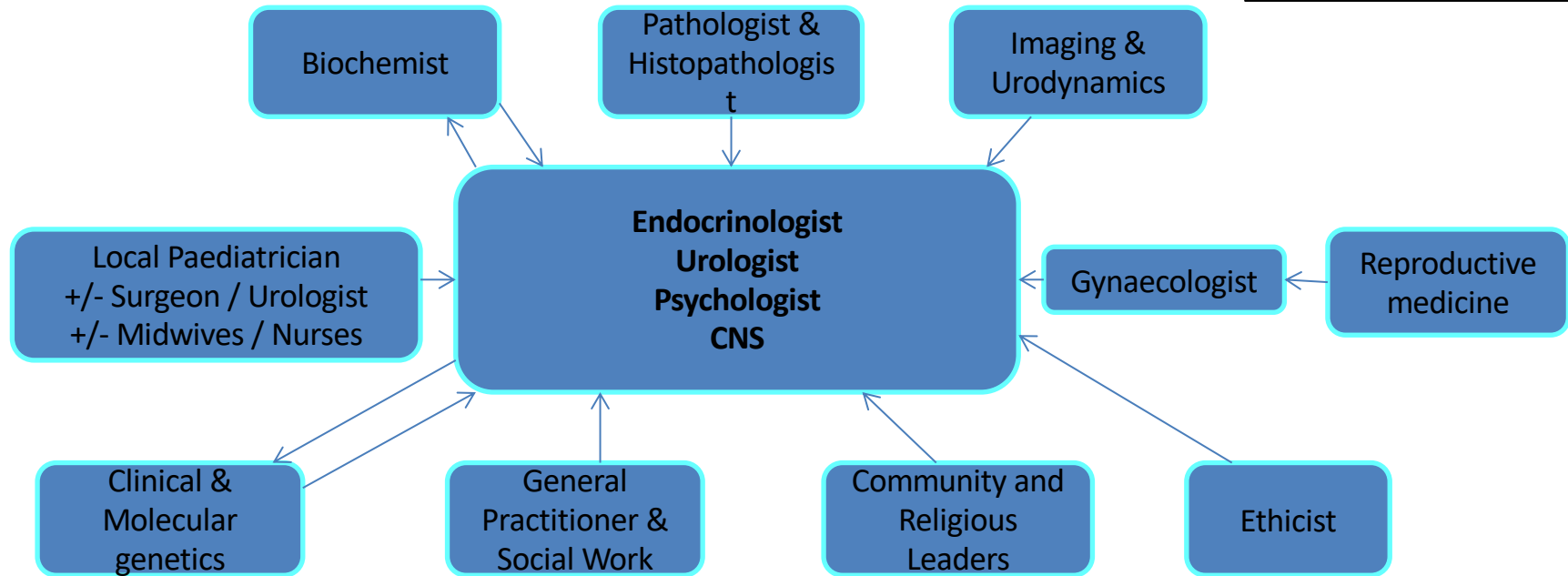


45X/46XY DSD

- Right gonad has a reasonable testis which has descended into a hemi-scrotum
- Left side gonad was intra-abdominal streak gonad
- Vaginal cavity present
- Raised a boy, gonads left insitu
- Re-presented in adolescence with a tumour arising from the streak gonad

- Wide range of phenotypes
 - 95% - normal male
 - SS and dysgenetic testes
 - Female phenotype
 - Features of TS (where karyotype has Y chromosome)
- Mixed gonadal dysgenesis
 - Asymmetrical appearance
- 75% have a uterus
- SS in 84%
 - GH therapy
- Abnormalities of urinary tract and CVS may be present
 - Similar to those of TS

DSD MDT team



Receiving a referral

- On call registrar receives a telephone call from referring Doctor from another hospital
- Alerts main DSD team
- Plan admission
 - Within 5 days if newborn
- Asks referring Dr to undertake specific investigations
- Plans investigations
 - Pelvic ultrasound, medical photography
- Clinical Nurse Specialist..

DSD referral form

- Emailed to lead consultant
- Filed in patient notes
- Filed in DSD file

NEW DSD REFERRAL CHECKLIST

Date: Receiving Dr: Consultant on Call:

Referring Hospital: Referring Dr Phone contact:

Patient Name : DOB: Gestational Age:

Patient history:

Family history:

Clinical status:

Investigations done:

Team to liaise with:

- ☐ Endocrine Consultant on call
- ☐ Kingfisher admissions and Sister Carly Hadfield
- ☐ Professor John Achermann
- ☐ Urology Consultant, Mr Imran Mushtaq or Miss Naima Smeulders
- ☐ DSD Clinical Nurse Specialist Kate Davies
- ☐ Dr Polly Carmichael, Consultant Psychologist
- ☐ Endocrine Registrars

Confirm:

Transport for baby / nurse escort

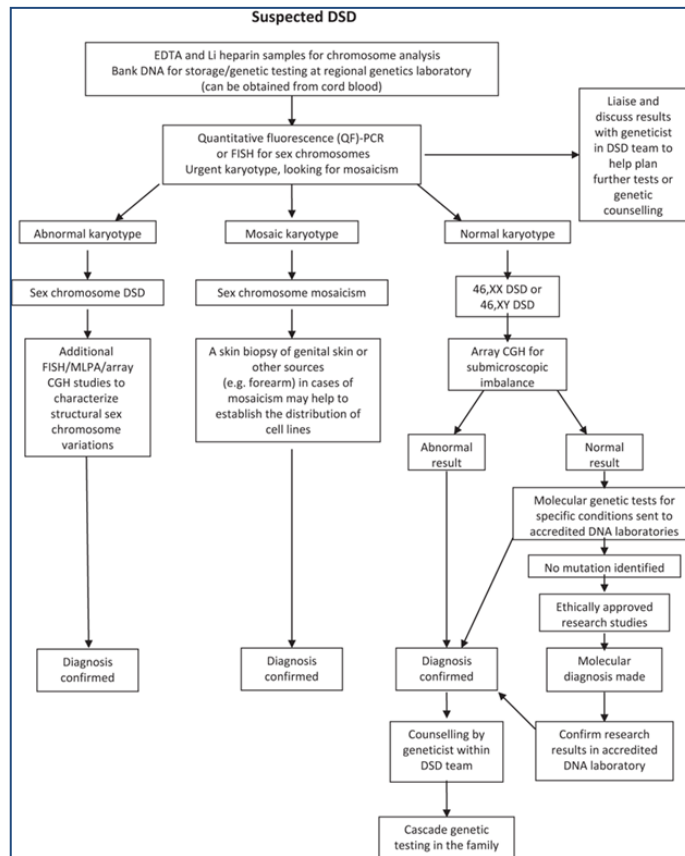
Stock of medication (LHRH / HCG / Synacthen) on ward

Interpreter

Breast pump / bottles / milk on ward

Plan:

Making the diagnosis



To ARRANGE:

- Pelvic and abdominal (renal) USS
- Clinical photography (if parents consent)
- General Bloods: U&E, Cortisol, ACTH, testosterone, inhibin B and AMH, FSH and LH
- USP (if not done or as back up sample); urinalysis for proteinuria (if not done)
- Bloods for DNA storage (if parents consent)
- Consider other investigations as required (e.g. synacthen test, LHRH test, PRA, aldosterone, prolactin/TFTs/IGF1)
- Cancel tests if samples not necessary (e.g. AMH in CAH) or duplicated (e.g. USP being done)

ON ADMISSION “MEET AND GREET” THE PARENTS, EXPLAIN WHAT WILL HAPPEN AND WHO THEY WILL SEE, AND FOCUS ON SUPPORT AS WELL AS THE PLANNED “TESTS” – appreciate how tired and stressed they are, and maintain their privacy; let them have time together to talk and reflect

46,XX

If CAH suspected (common):

PRIOR TO TREATMENT: Cortisol, PRA, Aldosterone, 17-OHP, A4, DHEAS, 11-deoxycortisol, USP
Short synacthen test only after day 3

Ovotesticular DSD (rare):

AMH, inhibin B, testosterone, consider early EUA and laparoscopy

Aromatase deficiency (v rare); also clitoromegaly of prematurity and structural variants

46,XY

Ensure **adrenal function** adequate (rare):

ACTH, cortisol, synacthen

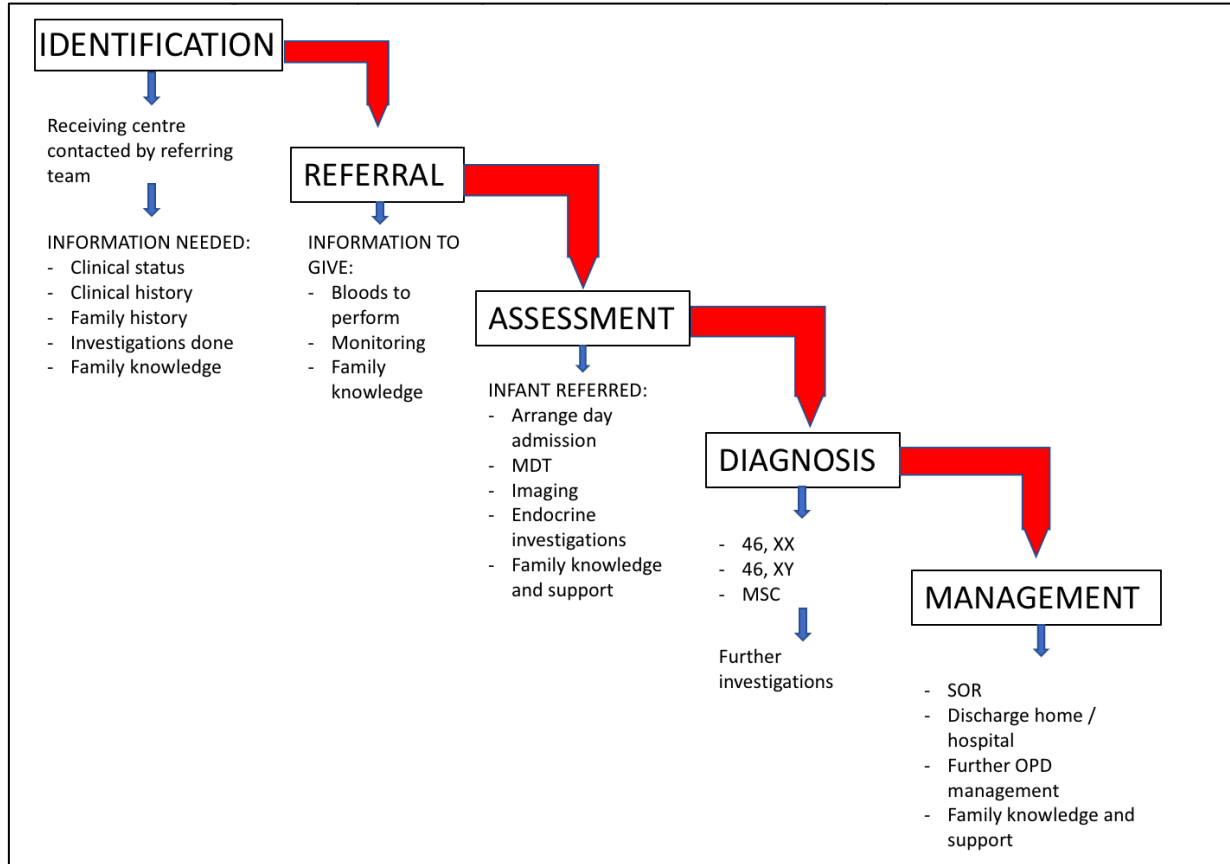
Is it **dygenesis, steroidogenic defect or androgen resistance?**

AMH, inhibin B, testosterone, LH/FSH, USP;
Consider 3 day/3 week hCG stimulation test

45,X/46,XY

AMH, inhibin B, testosterone, LH/FSH;
Consider 3 day/3 week hCG stimulation test or early EUA/laparoscopy;
ECHO, TFTs, renal USS, Turner screening, audiology etc

Diagnostic pathway



Monthly MDT meeting

- Every 2nd Monday of the month
- All meet
 - Lead Consultant Endocrinologist with DSD interest chairs the meeting
 - Registrars (Residents) present new cases
 - Discuss previous cases
 - Attended outpatients clinic
 - Attended the endocrine day case unit (Kingfisher)
 - Had EUA (Woodpecker)
 - Had surgery (Squirrel)
 - CNS
 - Makes notes on planned outcomes and proposed interventions.
 - CNS team ipad
 - Emailed to relevant people with tasks to be done

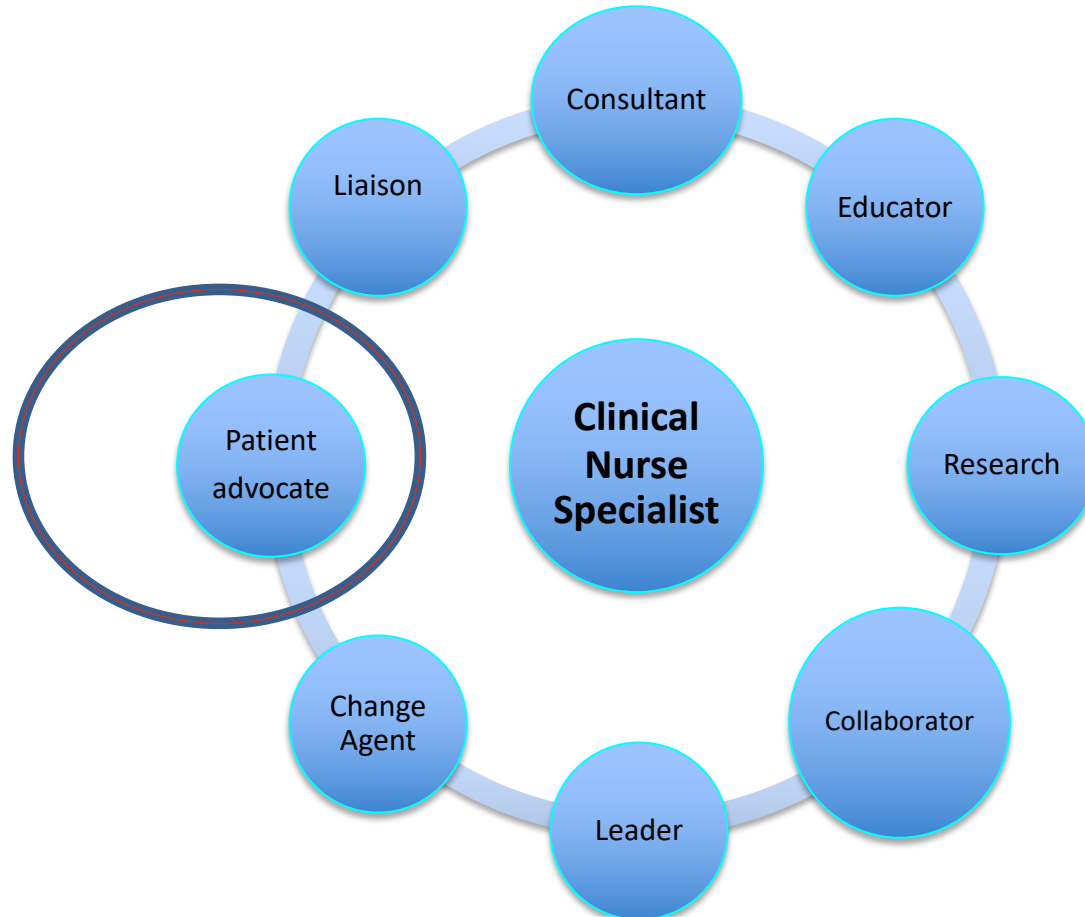
CNS DSD MDT notes

DSD MONDAY MDT ACTION PLAN

Date:

[illegible]

Clinical Nurse Specialist roles



CNS advocate role – at diagnosis

- Ensure referring team has parents admission leaflet
- Liaising with the MDT
 - From the referring team and also the team being referred to
 - Is the baby well / hospitalised
 - Are they requiring transport / nurse escort / will that nurse stay with patient
 - Liaising with the various members of MDT to arrange ward visit
 - Liaising with Biochemistry / Ultrasound / Photography
- Liaising with the ward
 - Ensure GnRH, Synacthen and HCG in stock on ward if need be
- Liaising with the parents!
- Prepare information packs for parents
 - DSD families leaflet
 - Cortisol deficiency booklets
 - CAH information
 - CNS contact details

- How is the baby feeding
 - Breast pump, bottles, quiet area available
 - Bottle feeding – enough milk
- Ensure parents bring
 - Phone chargers, nappies, wipes, books etc, lists of questions
 - Maternity notes, child health care notes, referral letters
 - Money for parking
- Can they speak English
 - Arrange interpreter, prepare translated information



Specifics..



- Making notes in MDT meeting
 - Ensuring full follow up
- Maintaining DSD database
- Consent forms for research
- Maintaining referrals folder and spreadsheets
- Arranging admissions
- Creating pathways, protocols and information sheets
- Teaching
- Presenting / lecturing
- There for the family on the day
- Support when discharged
- Liaison with Psychology – support group days

CNS advocate role - ongoing

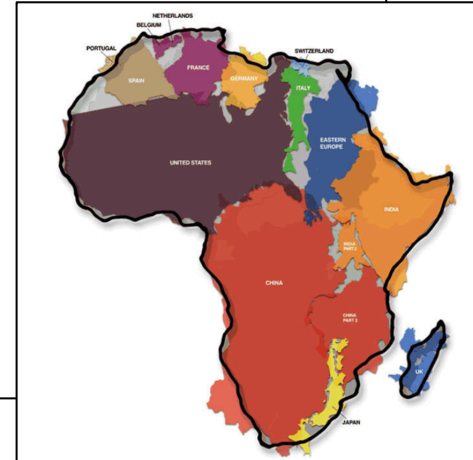
- Key liaison and support for family
- Involvement in support groups / support group days
- Be knowledgeable in specific condition and long term implications
 - Prepared for discussions on puberty and adolescence and beyond
- Liaise with adult DSD / gynaecology teams
- Patient and family empowerment



UK Statistics

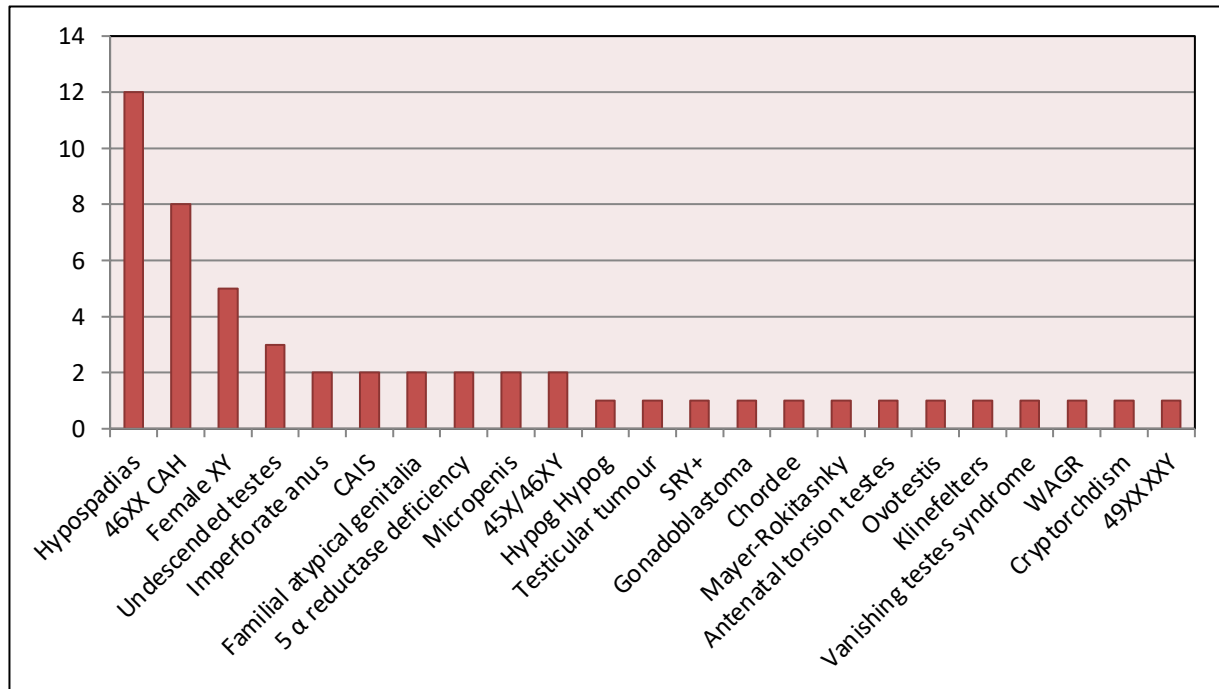
Relative sizes and population

- USA population: 318.9 million
- UK population: 64.1 million
- South Africa Population: 57.72 million
 - Capetown: 433, 688
 - London: 8.6 million
 - Los Angeles: 10 million

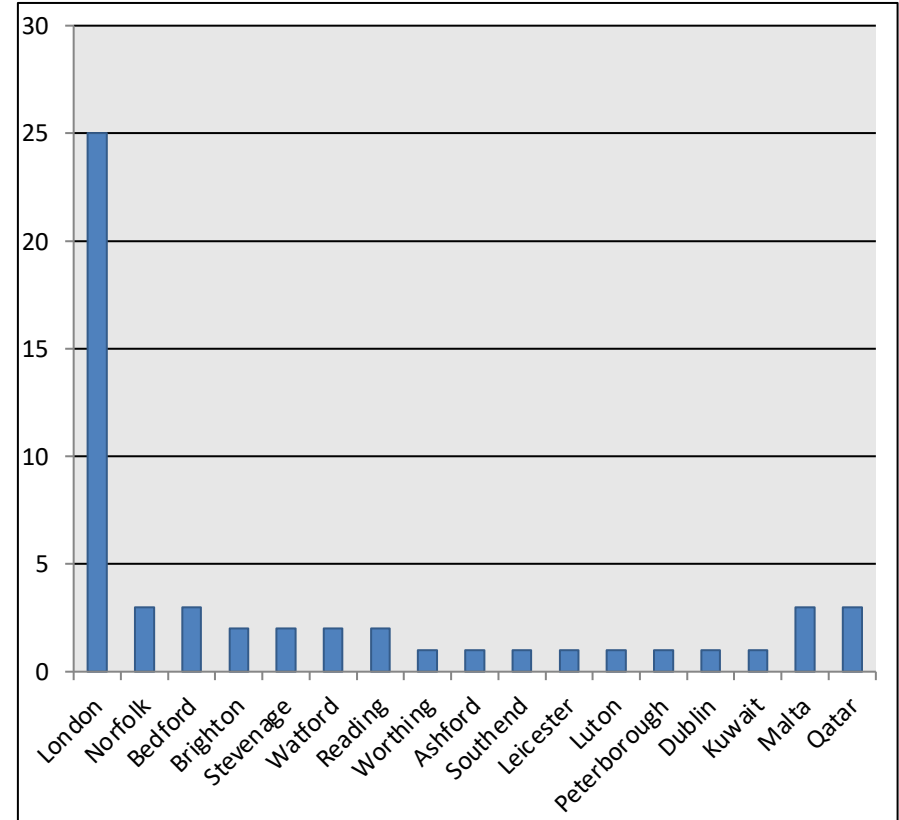
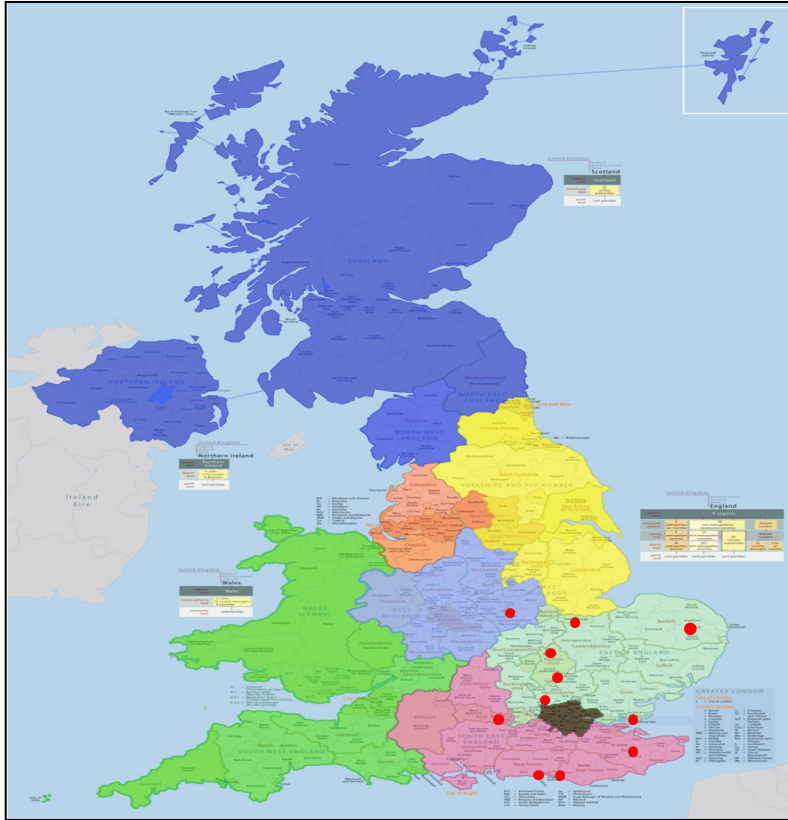


GOSH DSD diagnosis statistics - 2015

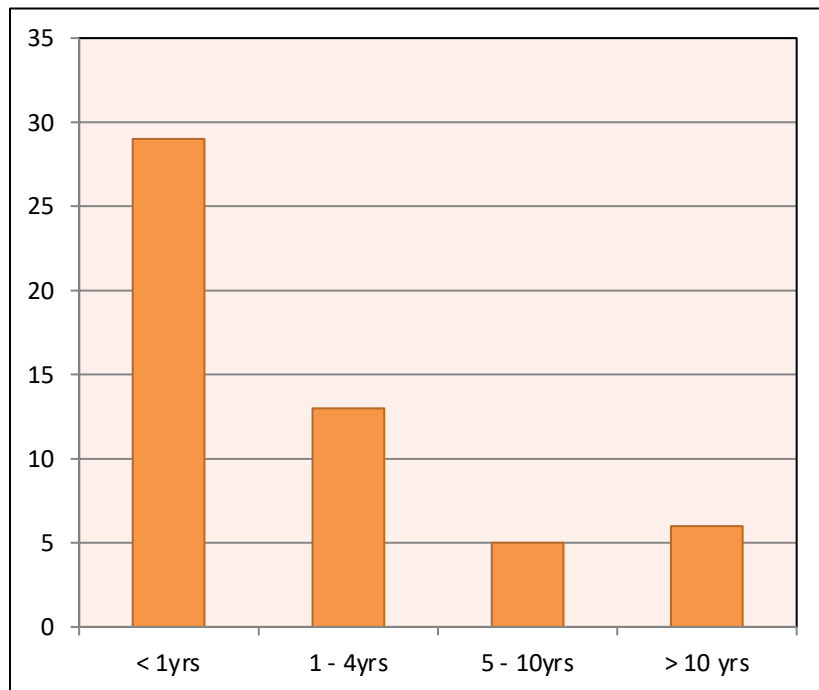
- 53 new referrals over one year
- Averaging 6 a month



DSD referral areas

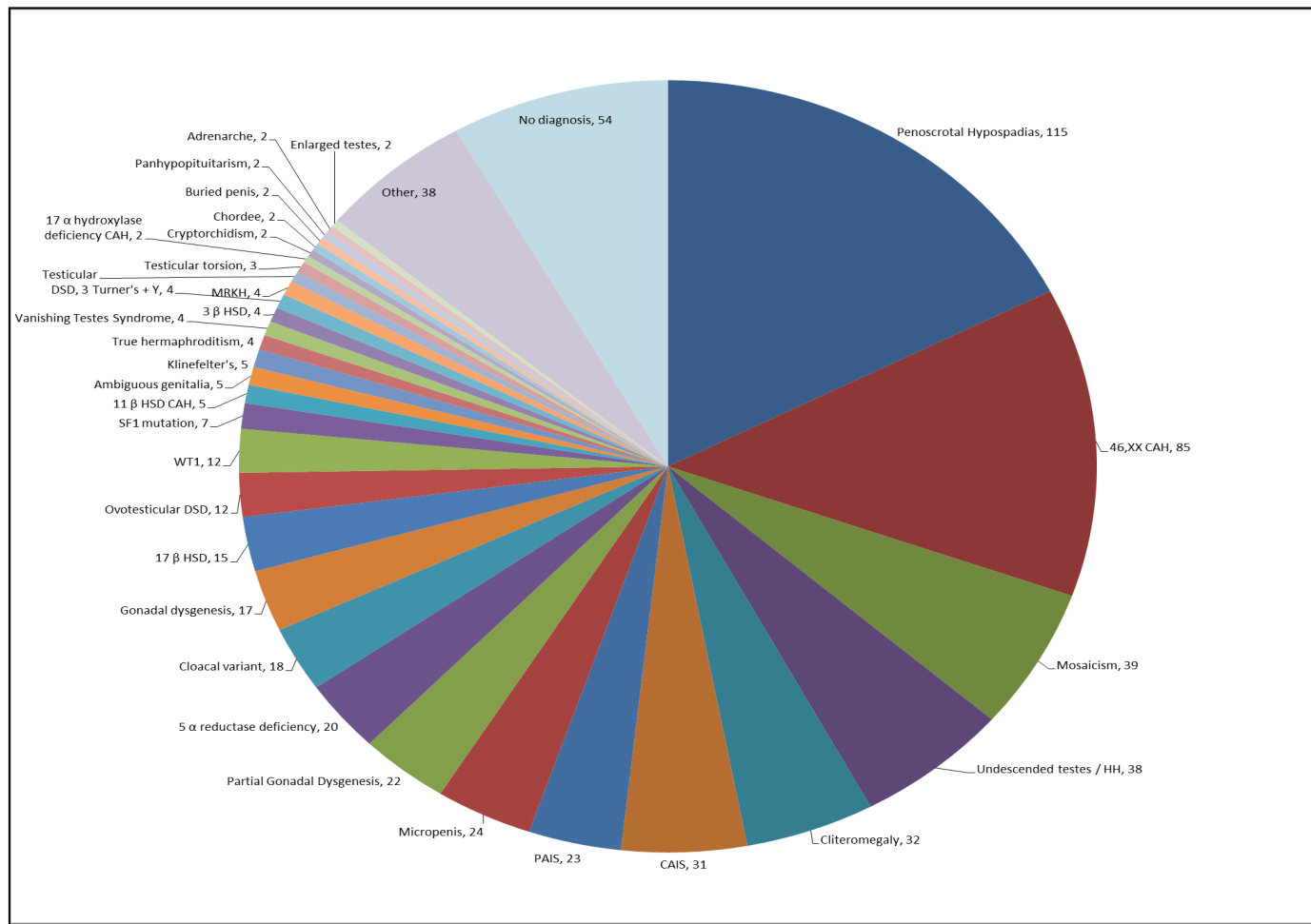


DSD ages of referral at GOSH



- Infants
 - Usually present with atypical genitalia
- Adolescents
 - Atypical sexual development
 - Micropenis
 - Cryptorchidism
 - Referrals from other centres
 - Previous hypospadias surgeries
 - Familial atypical genitalia
 - CAIS

GOSH DSD data over 21 years N= 657



International Statistics



South Africa

(Ganie et al, 2016)



- 416 children
 - 46 XY - 57.5%
 - Androgen synthesis action
 - Ovotesticular DSD
 - Single most common diagnosis amongst black African patients with ambiguous genitalia
 - 46 XX - 33%
 - CAH
 - MSC - 9.5%
 - TS – 2/3
 - Late presentation
- Lack of biochemistry tests
- Lack of advanced molecular techniques (WES)
 - Likely to alter classification of their cohort
 - WES
 - Can detect mutations in known DSD genes

DE GRUYTER

J Pediatr Endocrinol Metab 2016; aop

Yasmeen Ganie*, Colleen Aldous, Yusenantha Balakrishna and Rinus Wiersma

Disorders of sex development in children in KwaZulu-Natal Durban South Africa: 20-year experience in a tertiary centre

South Africa

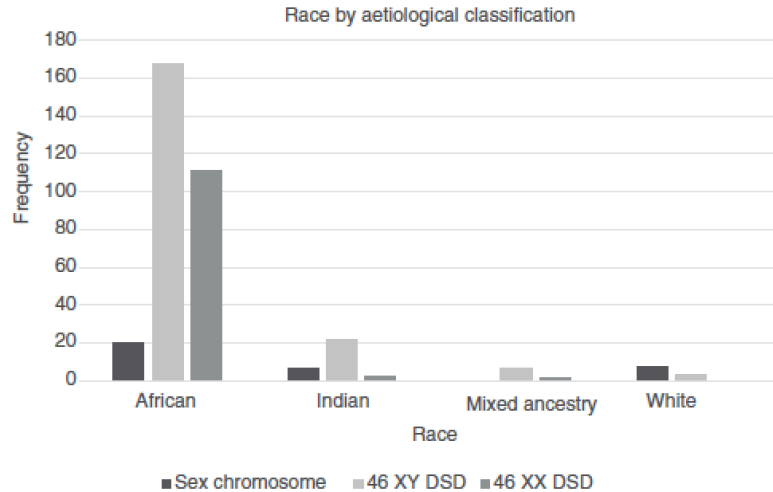


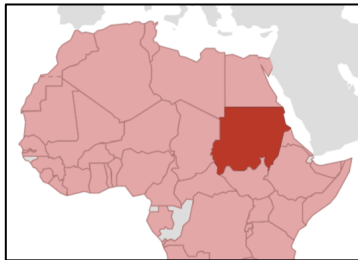
Figure 3: Race by aetiological classification (n= 346).

- Ethnicity
 - 86% African
 - 9% Indian
 - 3% White
 - 2% Mixed ancestry
- Statistically significant relationship
 - Different population groups
 - Diagnosis
- High prevalence of ovotesticular DSD in the African population
 - Further analysis necessary

Sudan

(Abdullah et al, 2012)

- 5 year retrospective study of PE clinic
- 156 DSD patients
 - 46 XX - 44%
 - CAH
 - 46 XY – 29%
 - AIS

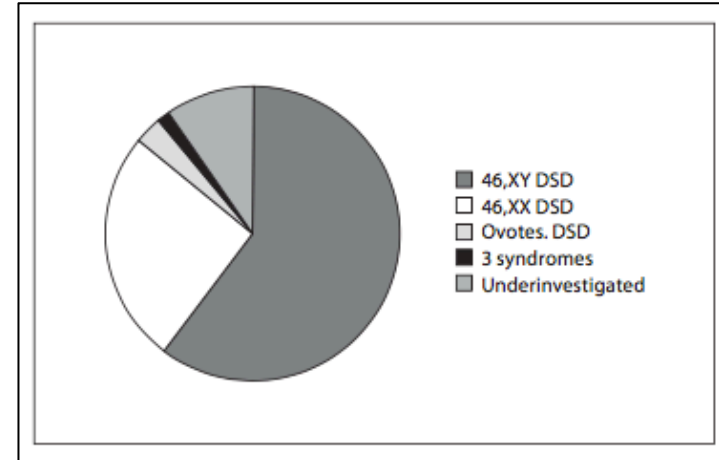


- 60% referred to specialized clinics
 - Some families refuse
 - Finance
 - Stigma
 - Some left without action
 - Aetiology spiritual
 - Not treated by Western medicine
- 70% deliveries at home
 - Midwives and young Drs not trained
- Sex assignment
 - Guesswork
 - Has to be done before naming ceremony
 - No later than 2 weeks
- SSIS
 - Sudan Scientific Intersex Society
 - MDT only in Khartoum
- Investigations
 - Costly (\$300 per patient)
 - Unavailable
- Early surgery opted for
 - Culture
 - Religious directives



Egypt *(Mazen et al, 2008)*

- 208 patients 2000 – 2005
 - 46 XY – 66%
 - 46 XX
 - 75% CAH
 - High rate of consanguinity – 61%
 - Preference of male sex of rearing
 - Regardless of karyotype
 - Despite severe genital ambiguity
 - Female infertility
 - » Precludes marriage
 - » Employment prospects



**HORMONE
RESEARCH**

Original Paper

Horm Res 2008;70:118–123
DOI: [10.1159/000137657](https://doi.org/10.1159/000137657)

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Differential Diagnosis of Disorders of Sex Development in Egypt

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Finland *(Kohva et al, 2018)*

- 550 patients 2004 – 2014
 - 46 XY – 54%
 - MSC – 37%
 - 46 XX – 9%
- Most common
 - Bilateral cryptorchidism
 - Klinefelter
 - TS (child health care clinic)
 - Mean age of diagnosis 4 years
 - Deceleration of growth
 - Finnish growth data?
 - National child measurement programme UK – Reception / Year 6
 - Finland – 20 height measurements from post birth – 12 years



E Kohva et al.

DSDs: timing of diagnosis and management

7:4

595–603

RESEARCH

Disorders of sex development: timing of diagnosis and management in a single large tertiary center

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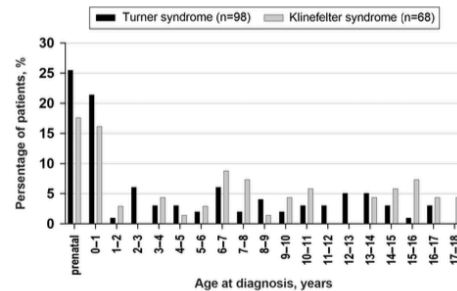


Figure 2
Percentage of TS (n=98) and KS (n=68) patients diagnosed per age group. Data obtained from patients visiting the outpatient clinics of a single tertiary center between 2004 and 2014 whose age at diagnosis was available.

Family Support - dsdfamilies

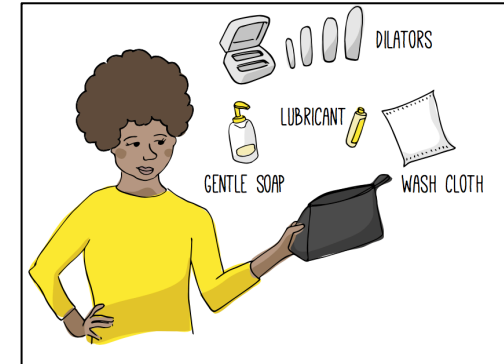
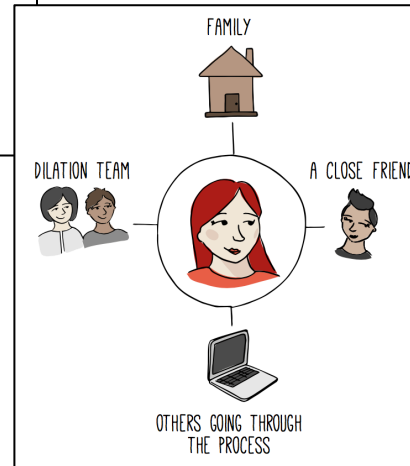
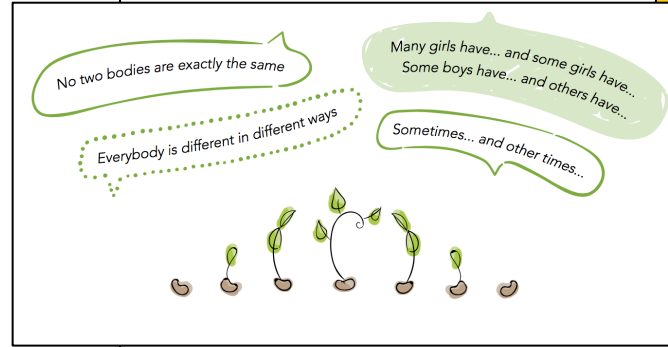


- dsdfamilies.org
- UK based support group
 - Information and support resource for families with children, teens and young adults with a DSD
 - Links to other support groups throughout the UK
 - CAH, TS, Hypospadias, Klinefelter, AIS
 - Links to international DSD support groups

- Advice
 - How to talk to others
 - How to talk with teenagers
 - Dilatation

Top Tips for Talking

about differences of sex development



TOP
TEN
TIPS
FOR DILATION

Conclusion..

- Brief overview of DSD service in the UK
 - Many more complex variants
 - Diagnosis
 - Management
 - Treatment
- International practice review
 - Cultural aspects important to consider
 - Practical elements – growth data
 - Access to molecular analysis and biochemical testing
 - Variance in diagnosis
 - Variance in classification
- Clinical Nurse Specialist role
 - Liaison
 - Organisation
 - Specifics of the role
- Future for more advanced nursing roles?
 - Midwives / Community Doctors
 - Further training

